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Bioelectrical Impedance Analysis Device: Measurement of Bioelectrical Tissue Conductivity in Dengue Patients

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Abstract: This paper describes and introduces a new approach to monitor dengue hemorrhagic fever using BIA technique. This technique is an *in vivo* technique where an approximately a small average constant current of 460 μA at single frequency, 50 kHz is applied through human body, and measure the body's resistance and reactance to that current via four-surface electrode. These measurements are combined with the patient data (i.e. age, sex, height and weight) to estimate mass and water compartments. The dengue's clinical studies in correlation with the BIA measurement have been conducted on 119 male and 91 female who are the DHF patients in Universiti Kebangsaan Malaysia, Hospital (HUKM) in Malaysia. The data obtained show that it is possible to predict a patient's condition; recovering or leading to hemorrhagic by monitoring the increasing trend of phase angle and reactance and the decreasing trend for the of ratio of extracellular to intracellular water (ECW/ICW) and ratio of extracellular body mass to body cell mass (ECM/BCM). Experimental findings show that bioelectrical tissue conductivity (BETC), as reflected by reactance is the key determinant indicator for monitoring the hemoglobin status in the DHF patients. Hence, this novel approach of BIA technique can provide rapid, non-invasive, and promising method for monitoring and evaluating the status of the DHF patients. *Copyright © 2011 IFSA.*

Keywords: Dengue fever, Dengue haemorrhagic fever, Haematological profile, Bioelectrical tissue conductivity, and bioelectrical impedance analysis device.

1. Introduction

Dengue fever (DF) ranks highly among the newly emerging infectious diseases in public health significance. Hence it is considered to be the most important arthropod-borne viral diseases. In

Malaysia, the disease is endemic but major outbreaks seem to occur at least once in every four years [1]. Dengue fever was first reported in Malaysia after an epidemic in Penang in 1902 [2, 3]. Since the early 1970s, the World Health Organization (WHO) has been actively involved in the developing and promoting strategies for treatment and control of dengue. In 1997, WHO published a second guide to the diagnosis, treatment and control of dengue haemorrhagic fever [4]. Dengue were reported throughout the year and started to increase from 1997 to 1998. In 1998, 27,373 dengue cases with 58 deaths were reported as compared to 19,544 cases with 50 deaths in 1997. This has shown an increase of 7,829 cases or 40.1 % over the number of cases in 1997 [5].

Dengue is a tropical viral infection, which affects hematological system. Thrombocytopenia and haemoconcentration (an increase in the hemotocrit of 20 % or more) representing the pathophysiological hallmarks of abnormal hemostatis and plasma leakage, respectively, are constant findings. Plasma leakages can lead to shock, which if uncorrected lead to tissue anoxia, metabolic acidosis and death.

Narayanan *et. al.* [6] noticed a higher proportion of tourniquet test positivity among children with shock. This also corroborates the finding by Bethell *et. al.* [7] regarding to the increased proportion of skin bleeding in patients with shock. They also investigation findings showed that platelet counts were significantly lesser in patients who developed shock. Bleeding has a correlation to platelet count only when it is less than 50,000/cu.mm. Balasubramanian *et. al.* [8] showed a haematocrit value of 34.8 % in children less than 5 years and 37.5 % in more than 5 years of age, good predictive indicators for haemo concentration in DHF.

This paper investigated that all descriptive analysis of haematological profile showed that constant abnormalities occur in PLT, AST, and ALT, while HCT only has a moderate elevation.

2. Experimental Set-up

Human body can be represented as consisting of resistances and capacitances. In a healthy living body, the cell membrane consists of a layer of non-conductive lipid material sandwiched between two layers of conductive protein molecules. Biologically, the cell membrane functions as a permeable barrier separating the intracellular (cytoplasm) and extracellular components (Fig. 1a). It is traversed by numerous water soluble proteins, thus producing pores through which water, ions and other chemicals can enter and exit the cell. Controlling the flow of these materials is essential to life. The cell membrane protects the interior of the cell while allowing passage of some materials to which it is permeable.

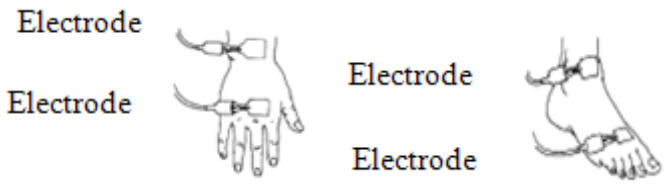

Fig. 1. Electrodes placement on the right side of the wrist and ankle. Electrodes A and B are current sources while electrodes C and D are voltage pick-up [17].

The cell membrane is composed mostly of a double layer of phospholipids, arranged tail to tail along the width of the cell membrane. This structure is called the lipid bilayer and is an electrical insulator (dielectric), as all fats and oils are. The head of the phospholipids are polar (carry a charge) and the

tails are non-polar. The heads interact with water, where the tail is repulsed by water aligning them tail to tail with the heads facing the outside and inside of the cell.

In this study, the BIA measurement were conducted by way of a tetrapolar configuration [12] using the BIA 450 analyzer. The four electrode technique used by this system largely avoids the aforementioned difficulties faced when using the two electrode technique. Four surface electrodes are used: two electrodes were placed on the subject's right hand, one at the base of knuckles and another slightly above the wrist joint. Another two electrodes were placed on the right foot, one near the base of the toes and the other slightly above the ankle joint.

The BIA 450 analyzer delivers constant current less than 1 mA at 50 kHz into the tissue via the electrodes attached at base of the knuckles and base of the toes (current electrodes between points A and B) and the signal was picked up by the other two sensor electrodes (voltage electrodes between points C and D) slightly above the ankle and wrist joints as shown in Fig. 1.

Ibrahim *et. al.* [14] describes a model for predicting haemoglobin (Hb) by using BIA in dengue patients. In this developed model, four predictors were found to be the best predictive factors for modeling Hb in dengue patients. Haemotocrit (Hct) and Hb (Hct is a approximately 3Hb [15] are related to each other, and Ibrahim *et. al.* [14] has shown that Hct was not suitable for modeling DF and DHF patients, thus Hb was chosen. BIA was sensitive in determining the hydrational profile in dengue patients.

2.1. Data Collection

The data were obtained from the previous work [16]. For the first group, the severity of the DHF is classified into grade I to IV, according to WHO recommendation [17]. Acute dengue infection was confirmed subsequently by the use of ELISA to detect elevated dengue specific IgM (primary infection) and IgG (secondary infection) [18]. Patient serum samples were tested for hemoglobin determination using an automated counter (Coulter STKS machine).

The second group is the control group for healthy female and male subjects. The second group of patients (control subjects) who do not have past medical history of dengue were recruited and studied using the same guidelines as in the BIA subject preparation used for the first group [16]. The BIA safety measurements procedure and other safety precautions were made known to the subjects and their informed consent was obtained from each subject prior to the BIA measurement.

For the control subject, the weight was taken only once throughout the whole study. However for subjects with dengue infection, the weight was measured daily until upon discharged.

2.2. Clinical Experiments

One of the clinical methods in making dengue diagnosis is to establish the clinical history-taking, physical examination and investigation. Each patient undergoes detailed history taking, physical examinations and blood investigations following their admission. Clinical evaluations and haematological investigations are conducted continuously until they are discharged.

The patients were also admitted at different stages of their illness, thus it is important to have the results of clinical signs and symptoms, blood investigations, and other analyses dated with a consistent and proper reference point [16]. Nevertheless, thorough documentation of symptoms and blood

investigations do not offer definitive advantage in the management and monitoring of dengue cases. A more useful measure is to develop a complete day-to-day profile of clinical manifestations and blood investigations made according to a proper reference point based on the 'Fever day' definition [16]. This is to ensure that the data used in the analysis will refer to a common reference point, regardless of how many days of fever the patient has experienced.

2.3. BIA Experiments

The bioelectrical impedance experiments are conducted using the bioimpedance analyzer. It is important to note that there is no historical or clinical evidence that bioimpedance testing is unsafe, even for pregnant women or persons with pre-existing heart conditions.

During the years 2001 and 2002, two hundred and ten adult patients aged twelve years old and above, with serological confirmation (WHO 1997) of acute dengue infection, admitted in HUKM, Malaysia were prospectively studied. At present, the knowledge acquisition to present pattern to classify the dengue infections is limited to the clinical symptoms and signs. Thus, only clinical symptoms were used as the input data for classify the dengue infections.

A total of one hundred and forty two volunteers with no past medical history were recruited and studied as the control subjects. For the control subject the weight was taken once, however for subjects with dengue infection the weight was measured daily until upon discharged.

The statistical analysis was performed using SPSS statistical package version 10.01 for Window 1998. Simple linear regression was used in the preliminary analysis for testing the significance of the variables. These variables were then included in the multivariate analysis. Multiple linear regression was used to analyze the control effects of the patient demographic and symptom variables and BIA parameters on Hb. The model was constructed in three steps as follows:

a. When correlation exits between variables, one or more variables were excluded for the multivariate analysis.
b. The demographic variables were first included in the model. Once the demographic predictors were identified, add in the BIA parameters and find, which of these parameters were important predictors.
c. The last step was to include symptom and find out whether with the addition of this predictor will make further significant contribution or not.

The last step was to include the symptom and find out whether with the addition of this predictor will make further significant contribution or not.

Only five variables are highly significant which gender, weight, reactance (Xc), vomiting and day of fever [14, 16, 19, 20].

3. Results Analysis

3.1. Data Analysis

This section presents the analysis of data collection that consists of two data groups' data which the first group is dengue data and second group is the control data.

3.1.1. Dengue Data

During the year 2001 to 2002, two hundred and ten adult patients aged 12 to 83 years old, suspected of DF and DHF admitted to the Universiti Kebangsaan Malaysia Hospital (HUKM), were monitored. The dengue infection was also confirmed serologically by detection of IgM antibody using the ELISA method. For all the 210 dengue patients studied, 119 (56.7 %) were male and 91 (43.3 %) were female. Distributions are shown in the majority of the confirmed patients were Malays (116 or 55.2 %), followed by Chinese with 60 patients (28.6 %), Indian with 15 (7.1 %) and others with 19 (9.0 %). Except for the Indians, the majority of patients were male. The female to male ratio for the Malay, Chinese, and Others was 0.8, 0.8, and 0.3 respectively.

The proportion of those who had DHF II is much higher (53.3 %) than DHF I (43.3 %), followed by DF (2.8 %) and DSS (0.5 %). The length of hospital stay duration ranged from 3 to 18 days, with an average of 5.3 days.

The sample size of the female was more than the male for DF by 4 patients. However, for DHF I the males exceeded the females by 11; the males increased by 22 compared to females in DHF II and there was only one female DSS patient. In the age distribution analysis, the patient majority were mainly in the 15-24 years group age (35.71 %), followed by the 25-34 years group age (25.24 %). Those aged between 35-44 years constituted 20 % for all cases. This indicates that the majority of the patients were teenagers and young adults, whom were more likely to be involved in outdoor activities and thus more likely to be exposed to the danger of dengue infection.

3.1.2. Demographic Data and Symptoms Analysis

The sample of 210 dengue patients consisted of 119 males and 91 females. The results indicate that almost (80 %) patients experienced anorexia on the day of admission, followed by petechial rash (55.7 %), nausea (35.7 %), body ache (34.8 %), headache (30.0 %) and others.

All patients had consistent symptoms with DF, which included abrupt onset of severe anorexia, petechial rash, nausea, body ache, headache, arthralgia, weakness in lower limb, dizziness and fainting, myalgia, macular and vomiting.

In the early stage, patients with DHF had similar symptoms to those with DF, but after several days the patients became irritable and gradually developed bleedings in a number of sites on their body, including gum bleeding, petechial rash (appears as pinpoint spots under the skin), and ecchymoses (confluent bleeding under the skin). DHF II is much more serious than DHF I with extra bleeding manifestations, including blood stained saliva and ecchymoses.

3.1.3. Bioelectrical Impedance Analysis

In the analysis of bioelectrical tissue conductivity (BETC) parameters for the healthy subjects, it was found that body capacitance (*BC*) and phase angle (α) were lower in the female subjects compared to their male counterparts (Table 2). On the other hand, resistor (*R*) and reactance (X_c) were higher in females than in males. A similar trend for the BETC parameters was also observed in dengue patients, where a higher α and *BC* values were found in males, and a higher *R* and X_c values were found in females. For example, on 'Fever day 0', the mean α for male was 6.69±0.91° and female was 5.45±1.02°, while the mean *BC* was 821.24±187.58 pF and 516.82±112.93 pF for males and females, respectively. However, the female *R* (592.14±93.90 Ω) and X_c (56.92±15.73 Ω) were higher than the male *R* (462.77±76.81 Ω) and X_c (54.02±11.15 Ω), respectively (Table 2).

3.1.3.1. Control Data

The healthy control data, a total of 144 volunteers with no past medical history were analyzed. The patients were between the ages of 13 to 60 years old, and 53 (37 %) were males and 91 (63 %) were females. The majority of the confirmed patients were Malays (95 or 66.0 %), followed by Chinese with 36 patients (25.0 %), Indian with 3 (2.0 %) and others with 10 (7.0 %).

In the age distribution analysis, the majority were mainly in the 15-24 years group age (35.71 %), followed by the 25-34 years group age (25.24 %). Those aged between 35-44 years constituted 20 % for all races.

3.1.3.2. Bioelectrical Impedance Analysis

Mean values of BETC descriptive analysis for both female and male dengue patients were always lower than the values for normal.

3.1.3.3. Experiment I for SPSS

Correlations between variables were analyzed using Spearman's correlation coefficient. It is a standardized measure of the strength of the relationship between two variables that does not rely on the assumptions of a parametric test. A matrix is displayed by giving the correlation coefficient between the two variables such as gender and height (0.647), underneath is the significant values of the coefficient (0.000) and finally the sample size (210). The significant value for this correlation coefficient is less than 0.05. Therefore, it can be concluded that there is a significant relationship between the gender and height.

Linear regression was used to identify the most significant variable among the bioelectrical impedance analysis parameters. The significant variables were resistance and reactance ($p<0.05$). Table 1 shows the model parameters. This model includes nine variables predicting the Hb, but only four variables are highly significant.

Table 1. Significant parameters for 210 dengue patients on day-of-admission.

Coefficients (a)

Model	Unstandardized Coefficients		Standardized Coefficients	t	Significance
	B	Standard Error	Beta		
(Constant)	6.012	3.75		1.603	0.112
GENDER	1.309	0.551	0.338	2.373	0.02
RISK	-0.241	0.32	-0.063	-0.753	0.453
HEIGHT	0.020	0.025	0.096	0.82	0.414
RACE	0.066	0.177	0.031	0.375	0.709
WEIGHT	0.029	0.014	0.264	2.059	0.042
RESISTANCE	-0.002	0.004	-0.105	-0.514	0.609
REACTANCE	0.047	0.019	0.327	2.48	0.015
VOMITING	1.178	0.493	0.191	2.388	0.019
ANOREXIA	0.156	0.341	0.035	0.458	0.648

a. Dependent Variable: Hemoglobin

The best model produced by the multilinear regression using four variables (gender, weight, reactance and vomiting) only yields an accuracy of 43 %. This model can be written as follows:

$$Hb = 6.012 + 1.309(gender) + 0.029(weight) + 0.047(reactance) + 0.19(vomiting) + \varepsilon \quad (1)$$

Where gender = 0 for female and 1 for male; *weight* is the weight of patients in kg; *react.* Is the reactance of patients in Ohm; vomiting = 1 for sign of vomit and 0 for no sign of vomit; ε is the error term.

3.1.3.4. Validation of Experiment 1 for Statistical Analysis

The actual Hb values were compared with the Hb model obtained as can be seen in Table 2. The calculated values from the Hb model match very well with the actual Hb values obtained from the blood sample. For example, a female patient with reactance of 77.70 Ω, weight of 38.00 kg and with sign of vomit had Hb of 12.30 g/dl based on her blood sample, *c.f.* 12.31 g/dl evaluated by the model. Case number 15, female patient with reactance of 52.90 Ω, weight of 70.00 kg and with no sign of vomit had Hb of 12.70 g/dl based on her blood sample, *c.f.* 12.56 g/dl evaluated by this model. Another example for male patient with reactance of 57.50 Ω, weight of 54.00 kg and with no sign of vomit had his Hb measured at 14.00 g/dl, *c.f.* 13.97 g/dl when evaluated using the Hb model. For case number 199, with reactance of 50.20 Ω, weight of 76.00 kg and with sign of vomit had Hb of 16.50 g/dl based on her blood sample, *c.f.* 15.22 g/dl evaluated by this model.

Table 2. Comparison between actual and predicted hemoglobin according to gender.

Case number	Gender	Weight (kg)	Reactance (Ω)	Vomiting	Actual hemoglobin (g/dl)	Predicted Hemoglobin (g/dl)	Residual (g/dl)
2	Female	38	77.70	1	12.30	12.31	0.01
15	Female	70	52.90	0	12.70	12.56	0.14
194	Male	54	57.50	0	14.00	13.97	0.03
199	Male	76	50.20	1	16.50	15.22	1.28

4. Conclusion

In general, this research has successful completed the experiments for modeling a non-invasive hemoglobin model using BIA parameters and physiological data to monitor the progression of dengue infections.

Using multivariate analysis, it was found that the work presented has successfully modeled the heamoglobin status by using selected physiological parameters such as gender, vomiting, weight and day of fever incorporate with and the BIA parameters, the body reactance.

The best model produced by the multilinear regression using four variables (gender, weight, reactance and vomiting). This model can be written as follow:

$$Hb = 6.012 + 1.309(gender) + 0.029(weight) + 0.047(react.) + 0.19(vomiting) + \varepsilon$$

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ABOUT THE CONFERENCE - AIM AND SCOPE

The European Conference on Organized Films 2011 is the 12th conference in a series of conferences devoted to current developments and progress in the field of thin organic films and nano-structures. It aims at promoting the understanding of films technologies, organization, and properties. It covers a wide range of subjects from fundamental research to applications. This includes material research and synthesis of organic molecules, polymers or hybrid materials with specific properties, the fabrication of thin films and nano-assamblies from Langmuir monolayers to highly organized multilayers and architectures or biomimetic systems, their patterning, and the study of the resulting structural, optical, electrical properties. Wide range of applications of thin films and nanostructures expanded the subject of the conference by including other subjects and advanced technologies such as organic and molecular electronics, photonics, photovoltaics, sensorics, biosensing and biomimetics. The ECOF 12 invites contributions that discuss these different aspects of thin films in science and technology and thus offers enormous opportunities for an intense exchange of new ideas and experiences. Welcome to Sheffield!

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- Lithography and nanopatterning

Properties

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- Electrical and magnetic properties
- Mechanical properties, rheology
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Sensors & Transducers Journal

Guide for Contributors

Aims and Scope

Sensors & Transducers Journal (ISSN 1726-5479) provides an advanced forum for the science and technology of physical, chemical sensors and biosensors. It publishes state-of-the-art reviews, regular research and application specific papers, short notes, letters to Editor and sensors related books reviews as well as academic, practical and commercial information of interest to its readership. Because of it is a peer reviewed international journal, papers rapidly published in *Sensors & Transducers Journal* will receive a very high publicity. The journal is published monthly as twelve issues per year by International Frequency Sensor Association (IFSA). In additional, some special sponsored and conference issues published annually. *Sensors & Transducers Journal* is indexed and abstracted very quickly by Chemical Abstracts, IndexCopernicus Journals Master List, Open J-Gate, Google Scholar, etc. Since 2011 the journal is covered and indexed (including a Scopus, Embase, Engineering Village and Reaxys) in Elsevier products.

Topics Covered

Contributions are invited on all aspects of research, development and application of the science and technology of sensors, transducers and sensor instrumentations. Topics include, but are not restricted to:

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- Digital, frequency, period, duty-cycle, time interval, PWM, pulse number output sensors and transducers;
- Theory, principles, effects, design, standardization and modeling;
- Smart sensors and systems;
- Sensor instrumentation;
- Virtual instruments;
- Sensors interfaces, buses and networks;
- Signal processing;
- Frequency (period, duty-cycle)-to-digital converters, ADC;
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